UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/010,377	01/21/1998	S.A. RUBIN	015270-00430	8602

7590 07/29/2002

Teresa Stanek Rea, ESQ
Burns Doane Swecker & Mathis, LLP
1737 King Street, Suite 500
Alexandria, VA 22314

EXAMINER
GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
1644	28

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/010377	Applicant(s) RUBIN
	Examiner GIMBEL	Art Unit 1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 3/27/01; 11/29/01; 12/5/01/3/6/02

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) 1-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on 1/14/98 is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

#28

DETAILED ACTION

1. The request, filed 3/27/01 (Paper No. 19), for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/010,377 is acceptable and a CPA has been established
An Office Action on the CPA follows.

Applicant's amendment, filed 3/15/02 (Paper No. 26), has been entered.
Claims 18-19 have been added.

Claims 1-19 are pending.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

The rejections of record can be found in the previous Office Actions (Paper Nos. 9/12/17).

Applicant's arguments and the examiner's rebuttal are of record.

This Office Action will be in response to applicant's Remarks in CPA submission in conjunction with the Karlik declaration under 37 C.F.R. § 1.132, filed 12/5/01 (Paper No. 24).

3. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84.
Please see the form PTO-948 previously sent in Paper No. 12.
Applicant is reminded to indicate Figures 3A, 3B and 3C in the Brief Description of the Drawings.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES
A. Correction of Informalities -- 37 CFR 1.85
New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.
All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

4. Claims 1-8, 11, 14-17 and newly added claims 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating viral encephalitis with "antibodies that bind the alpha-4 subunit of VLA-4" and peptides having the formula set forth in SEQ ID NOS: 3/4/5 as disclosed on pages-10 of the instant specification, does not reasonably provide enablement for any "agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments and the examiner's rebuttal are of record.

It does not appear that applicant's Remarks in CPA submission address the rejection under 35 U.S.C. 112, first paragraph, scope of enablement.

Applicant argues that pages 9-10 and 15 provides for agents that specifically inhibit VCAM-1 binding to the α4 subunit of VLA-4.

Upon reconsideration of applicant's arguments and the disclosure of particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification; such peptides are considered enabled.

It is noted that these peptides disclosed in WO 96/01644.

However, should recite these peptides in the claims.

However, applicant appears to rely upon the disclosure of other peptides disclosed in WO 96.22966; WO 96/20216; WO 96/00581 and WO 9606108 as well as U.S. Patent No. 5,510,332 (1449; #AB).

Here, it appears applicant is attempting to incorporate by reference essential subject matter to non-U.S. Patents.

In contrast to relying upon either SEQ ID NOS: 3/4/5 or U.S. Patent No. 5,510,332 which are disclosed in the instant specification as filed; applicant is attempting to incorporate by reference essential subject matter either to non-U.S. Patents or to material not disclosed in the application as filed.

The following of record is noted.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

As pointed out previously for example; it has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Applicant has not enabled structurally related nor unrelated compounds comprising "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin" or "any agent that specifically bind the alpha-4 subunit of VLA-4". Such structurally unrelated compounds/agents would be expected to have greater differences in their activities. There is insufficient direction or objective evidence as to how to make and to how to use any agent that "inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin" or "that specifically bind the alpha-4 subunit of VLA-4", for the number of possibilities associated with the myriad of direct and indirect effects associated with various adhesion pathways or molecules and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). The inherent difficulties of this approach include development of serum sickness after injection of foreign protein, diminishing therapeutic effects after prolonged therapy and the potential for promotion of infection.

The success of state of the art structure-based strategies for inhibitor design is highly unpredictable. For example, Kuntz (Science 257:1078-1082, 1992) on page 1080, column 3, discloses that as little as 2% of compounds predicted to inhibit specific enzymatic or receptor systems actually show inhibition in the micromolar range. Kuntz further discloses that "optimization" of these compounds has proven even more problematic. Therefore, in view of the unpredictability in the art, and in view of the insufficient guidance and working examples in the specification, the quantity of experimentation required by one skilled in the art to practice the invention undue.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin"or "that specifically bind the alpha-4 subunit of VLA-4", and still provide or maintain sufficient activity to treat viral encephalitis would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Again, applicant is invited to recite the particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification into the claimed methods.

Otherwise, applicant's arguments have been fully considered but are not found convincing essentially for the reasons of record, as the claims read on any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

Applicant's arguments have not been found persuasive with the breadth of "agents that inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

5. Claim 19 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

6. Claims 1-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449) and further in view of Ashwell et al. (U.S. Patent No. 6,291,453).

Claims 1-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449) and further in view of Ashwell et al. (U.S. Patent No. 6,291,453)., as applied to claims 1-19 above
and in further view of the art known role or etiology of various viruses inducing encephalitis, as evidenced by Planz et al. (J. Virol. 69: 896-903, 1995; 1449)
AND/OR
the role herpes viruses in multiple sclerosis, as taught by Sanders et al. (Archives of Neurology 53: 125-133, 1996) AND/OR Editorial (Archives of Neurology, 53: 123-124, 1996)

Applicant's arguments and the examiner's rebuttal are of record.

Applicant's Remarks (CPA submission) in conjunction with the Karlik declaration under 37 C.F.R. § 1.132, filed 12/5/01 (Paper No. 24), have been fully considered but has not been found convincing for the reasons of record and those set forth herein.

Applicant submits with the Karlik Declaration that the animal models disclosed in the present application is different from the models discussed in the cited art, the animals models discussed in the cited art are not predictive of the efficacy of anti-VLA-4 agents in viral encephalitis in the absence of multiple sclerosis and the animal model of the subject application is predictive that agents to VLA-4 are useful in treating simple viral encephalitis.

Karlik points out that the animal models of the cited references rely upon the effects of anti-α4 in inhibiting inflammation due to EAE, a syndrome simulating multiple sclerosis. Also, this model simulates autoimmune diseases which does not result from viral sources. Karlik noted that viral inflammation could not have been addressed in the EAE model of Bendig et al. And that the results of the EAE models do not directly address the ability of anti-α4 antibodies to treat inflammation due exclusively to viral infection.

Karlik points out that the present inventors employed an animal model in which inflammation is solely the result of viral infection, wherein the results indicate that treatment with anti-α4 antibodies is effective in suppressing the harmful effects that keep viral replication in check without significantly suppressing the beneficial effects that keep viral replication in check. For example, treating with anti-α4 antibodies was effective in prevent or ameliorating immune-mediated CNS damage following viral encephalitis in rats (pages 23-27) and that despite blocking the immunopathological immune response to viral encephalitis the treatment did not cause enhanced viral replication (pages 27-28). .

Karlik states that the combination of the beneficial and harmful consequences of viral infection-induced inflammation create uncertainty in the predictability of the immunosuppressive agents that would be useful in inhibiting such inflammation. For example, if treatment with an immunosuppressive agent increased the extent of viral infection as a result of decreased immune surveillance, the agent could effectively cause an increase in the damage to the subject.

Applicant's comments with respect to expert opinion in conjunction with the Utility Guidelines and In re Soni 34 USPQ2d 1684, 1688 (Fed. Cir. 1995) are acknowledged. However the rejections are not based upon Utility. Also, the rejections of record are based on the totality of the record.

Applicant has argued the presently claimed methods are direct ed to treating viral encephalitis by blocking adhesion of t cells with brain endothelial cells. Applicant has relied upon the complexity of studies of Borna disease (e.g. pages 4-5 of the instant specification) to indicate the lack of predictability of blocking binding of α4-integrin on T cells to VCAM-1 on brain endothelial cells. . Applicant further has argued that Bendig and Soilu-Hanninen et al. do not provide sufficient motivation in treating viral encephalitis.

While it is noted that the claimed methods are distinguished from multiple sclerosis; it appears the combined teachings are consistent with the role of T cells in viral inflammation encompassing viral encephalitis and that there was sufficient motivation and expectation of success in inhibiting T cells via blocking VLA-4:VCAM-1 interactions to treat said viral inflammatory conditions wherein T cells contribute to the inflammation at the time the invention was made.

Also, it is noted that newly added Ashwell et al. (U.S. Patent No. 6,291,453) teaches that inhibitors for VLA-4:VCAM-1 interactions, including those inhibitors that bind α4 are useful to treat inflammatory brain disorders, such as multiple sclerosis, viral meningitis and encephalitis. Therefore, Ashwell et al. provides for treating various inflammatory brain disorders, including viral encephalitis. Also, the prior art is not limited to treating multiple sclerosis only as the brain inflammatory disorder.

As pointed out previously, Bendig et al. teach using VLA-4α-specific antibodies, including the 21.6 specificity to treat encephalitis (see entire document, including VII. Methods of Treatment on columns 14-16) treating encephalitis and multiple sclerosis).

Also, as pointed out previously; Soilu-Hanninen et al. teach using VLA-4α-specific antibodies to treat virus-facilitated EAE, including its implications relapses triggered by viral infections in multiple sclerosis and by arboviruses (see entire documents). Soilu-Hanninen et al teach that viral infections serve as triggers of relapse phases of multiple sclerosis and the relationship of viral infection with the facilitation of leukocyte entry into the CNS (see entire document, including the Abstract, Introduction and Discussion, 1997).

In contrast to applicant's arguments on lack of predictability; Planz et al. teach the role of T cell subsets in Borna disease virus induce progressive encephalitis (see entire document).

Also, it is noted Planz et al. Borna virus disease after cyclophosphamide-induced immunosuppression were treated with antibodies directed to T cells (anti-CD8 antibodies) developed neither encephalitis nor disease (see entire document, including the Abstract). Planz et al. state that the presence of $CD8^+$ T cell apparently correlated with the development of neurological symptoms (see Abstract and Discussion).

Therefore, the prior art provided an expectation of success in blocking T cells wherein the treated individuals developed neither encephalitis nor disease. Even though the anti-CD8 antibodies target cells involved in the immune response, the further treatment of anti-CD8 antibodies did not exacerbate the Borna virus disease, given the role of T cells in the development of neurological symptoms associated with virus-induced progressive encephalitis.

Also, both Archives of Neurology citations disclosed that herpes is a common neurotropic virus which was present in more multiple sclerosis patients than control cases (see entire documents).

Therefore, given the clear teaching of treating encephalitis and/or multiple sclerosis with VLA-4α-specific antibodies, as well as the combined teaching that viral infections can serve as triggers of relapse phases of multiple sclerosis as taught by Soilu-Hanninen et al. Or that viral infections can lead to encephalitis as taught by Planz et al. or that herpes viruses are associated with multiple sclerosis; treating patients populations encompassing symptomatic, asymptomatic and pediatric patients would have been targeted by the ordinary artisan at the time the invention was made. Also, given the viral component of encephalitis sclerosis; the ordinary artisan would have provide standard anti-inflammatory and antiviral treatment in addition to VLA-4α-specific antibodies at the time the invention was made to inhibit the T cell component of the inflammatory disease.

Applicant's arguments are not found persuasive.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Serial No. 09/010377
Art Unit 1644

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
July 29, 2002
PHILLIP GAMBEL